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Serum Electrophoretic Changes in Patients with Pulmonary Tuberculosis, Chronic Bronchitis, Bronchiectasis, and Asthma

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SERUM ELECTROPHORETIC CHANGES IN PATIENTS WITH PULMONARY TUBERCULOSIS, CHRONIC BRONCHITIS, BRONCHIECTASIS, AND ASTHMA

by

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Thesis directed by Assistant Clinical Professor Irving Kass

Patients with multiple myeloma, Hodgkin's disease and other lymphomas have gamma globulin peaks in their serum electrophoretic pattern much above normal; usually, they also have histories of repeated infections, as well as poor antibody response to specific antigens. High serum gamma globulin levels have been noted by some investigators in patients with a variety of diseases associated with chronic infections--including certain chest diseases. The present study consisting of 254 patients and forty-one controls, showed a statistically significant elevation of the serum gamma globulin levels in patients with tuberculosis (active or inactive), bronchiectasis, chronic bronchitis, and the infectious type of asthma. On the other hand, patients with allergic asthma or with mixed-type asthma had gamma globulin levels within the normal range.

Since some of the patient subjects had high serum gamma globulin levels, it was hypothesized that they might show (as do patients with multiple myeloma, Hodgkin's disease, and other lymphomas) poor antibody response to specific antigens. In order to test this hypothesis, a controlled study was undertaken in which eleven patients with chronic bronchitis and a history in common of repeated respiratory infections and five "normal control subjects" were immunized with diphtheria toxoid, staphage lysate, mumps, influenza, and typhoid-paratyphoid vaccines. Although incomplete, the results obtained from this small

series of patients suggest that a factor other than antibody response seems to play an important role in the increased susceptibility of these patients to infections.

This abstract of about 235 words is approved as to form and content.
I recommend its publication.

Signed Joseph H. Holmes
Instructor in charge of dissertation

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INTRODUCTION

The simplicity of the technique of paper electrophoresis (1-3), when compared with the classic Tiselius technique (4-7), has led to its wider application in the separation and measurement of the various protein fractions of serum and plasma. For the past five years serum electrophoretic studies have been done routinely on all patients admitted to the chest service of the National Jewish Hospital at Denver. The purposes of this thesis are to discuss the data obtained from the various patient groups, and to review the literature relating to the general use and clinical application of the serum electrophoresis technique, with particular emphasis on the role of serum electrophoresis in the pulmonary diseases.

A study of the antibody response to specific antigens was attempted in a few patients with a clinical diagnosis of chronic bronchitis.

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MATERIAL

Serum electrophoretic studies were done on 295 adults. (Table I) The patients ranged in age from 16 through 75 years. For this study they were divided into eight groups: active pulmonary tuberculosis, 135 (Appendix A); inactive pulmonary tuberculosis, 34 (Appendix B); chronic bronchitis, 14 (Appendix C); bronchiectasis, 12 (Appendix D); infectious asthma, 10 (Appendix E); allergic asthma, 20 (Appendix F); and asthma, mixed type (allergic and infectious components), 29 (Appendix G). All forty-one subjects used as controls (Appendix H) had normal chest x-ray films and no histories of known chest disease.

Assignment of a patient to a clinical group was based on a thorough study, including history, chest x-rays, sputum studies, and, if indicated, bronchoscopy, bronchograms, skin, conjunctival and inhalation tests.

Patients with active tuberculosis, regardless of extent of disease, were put into one group; patients with inactive tuberculosis, into a second group.

Patients in the chronic bronchitis group were those with recurrent, long-standing, low-grade infection of the respiratory tract, producing yellow or yellowish-green sputum, with or without fever.

Patients in the bronchiectasis group were assigned to it on the basis of bronchographic confirmation.

Patients put in the bronchial asthma group were those who had

recurrent attacks of wheezing, cough and shortness of breath. A thorough cause-and-effect history of the patient, allergy skin tests, and conjunctival and inhalation tests were evaluated in order to differentiate the allergic from the infectious and the mixed type of asthma. Any classification is bound to provoke controversy; however, to avoid confusion, "asthma" was divided into these three categories: infectious, allergic, and mixed type.

TABLE I

DISTRIBUTION OF PATIENTS

Pulmonary Tuberculosis, Active	135
Pulmonary Tuberculosis, Inactive	34
Chronic Bronchitis	14
Bronchiectasis	12
Bronchial Asthma (Infectious)	10
Bronchial Asthma (Allergic)	20
Bronchial Asthma (Mixed)	29
Total	254
Controls	41
Grand Total	295

METHOD

Venous blood was drawn before breakfast and allowed to clot at room temperature. The tubes containing the clotted blood were centrifuged at low speeds, and the clear unhemolyzed sera were decanted. Whenever possible, the electrophoretic patterns were run the same day. If not, the sera were kept in liquid state at 0° to 2°C. Approximately two ml. of serum was required for each electrophoretic analysis.

These analyses were made with the Spinco Model R Paper Electrophoresis System. (8) Ten microliters (0.01 ml.) of serum was applied to a three-millimeter Whatman paper strip suspended in the electrophoresis cell vessel containing barbital buffer (pH 8.6). A constant output rectifier supplied five milliamperes of current to the cell vessel for 16 hours at room temperature. The electrophoretic patterns so obtained were dried for 30 minutes in an oven preheated to between 120° and 130°C. The strips were then stained with bromphenol blue and zinc sulfate and fixed with sodium acetate. The stained strips were scanned by means of a Spinco Analytrol, which is a combined scanner and integrator, and the per cent distribution of the protein was calculated. Serum total proteins were determined by the biuret method. (9)

The different fractions of the total protein were converted into grams/100 ml., and the mean standard deviation and the mean standard error for each of the eight groups computed. The T-test for unpaired variates was used to evaluate the differences between each of the seven

disease groups and the control group[1]. If the probability (P value) was greater than 0.05, no significant difference between the different groups was assumed. A probability (P value) of less than 0.05 was interpreted to mean that a statistically significant difference existed.

1. Volk, William. Applied Statistics for Engineers. N. Y., McGraw-Hill Book Co., Inc., pp. 115--116, 1958.

RESULTS

Serum Total Proteins

In 29 cases of bronchial asthma (mixed type), a statistically significant decrease of serum total proteins was noted when this group was compared with the control group. A borderline decrease of serum total proteins was noted in fourteen patients with chronic bronchitis. No significant change was noticed in patients belonging to the other groups studied when compared with the control group. (Table II)

Serum Albumin

Significant reduction of serum albumin was noticed in cases of active and inactive pulmonary tuberculosis, and chronic bronchitis when compared with the control group. There was borderline reduction in cases of bronchiectasis and bronchial asthma (mixed type). No significant difference was found between the disease and the control groups in cases of bronchial asthma of the allergic and the infectious types. (Table III)

Alpha-1 Globulin

No statistically significant changes were noticed in any of the groups when compared with the control group. (Table IV)

Alpha-2 Globulin

No statistically significant changes were found in any of the seven groups when compared with the control group. (Table V)

Beta Globulin

No statistically significant difference was noticed in any of the seven groups when compared with the control group. (Table VI)

Gamma Globulin

There was a marked and statistically significant rise of gamma globulin in cases of bronchiectasis when compared with the control group. Statistically significant elevations of gamma globulin levels were also noticed in cases of active and inactive pulmonary tuberculosis, chronic bronchitis, and asthma of infectious type. Cases of the allergic and mixed type of asthma showed no statistically significant changes in the gamma globulin levels. (Table VII)

TABLE II

THE SERUM PROTEIN LEVEL IN EACH GROUP AS COMPARED TO THE CONTROL GROUP

	Number of Cases	Mean (Gm/100cc)	Standard Deviation (±)	Significance (P)*
Pulmonary Tbc., Active	135	7.51	0.76	P > 0.1
Pulmonary Tbc., Inactive	34	7.39	0.53	P > 0.05
Chronic Bronchitis	14	7.12	1.01	P < 0.05
Bronchiectasis	12	7.33	0.59	P > 0.1
Bronchial Asthma (Inf.)	10	7.35	0.66	P = 0.2
Bronchial Asthma (Allergic)	20	7.45	0.86	P > 0.2
Bronchial Asthma (Mixed)	29	7.06	0.92	P < 0.001
Controls	41	7.69	0.76	--------
	295			

* P value < 0.05 shows a significant difference between the groups compared.

TABLE III

THE SERUM ALBUMIN LEVEL IN EACH GROUP COMPARED TO THE CONTROL GROUP

	Number of Cases	Mean (Gm/100cc)	Standard Deviation (±)	Significance (P)*
Pulmonary Tbc., Active	135	3.28	1.48	$P < 0.001$
Pulmonary Tbc., Inactive	34	3.63	0.80	$P < 0.02$
Chronic Bronchitis	14	3.11	1.02	$P < 0.01$
Bronchiectasis	12	3.38	1.32	$P > 0.05$
Bronchial Asthma (Inf.)	10	3.55	1.34	$P > 0.2$
Bronchial Asthma (Allergic)	20	3.98	1.06	$P > 0.3$
Bronchial Asthma (Mixed)	29	3.72	0.93	$P > 0.05$
Controls	41	4.33	0.98	-------
	295			

* P value < 0.05 shows a significant difference between the groups compared.

TABLE IV

THE SERUM ALPHA-1 GLOBULIN LEVEL IN EACH GROUP AS COMPARED TO THE CONTROL GROUP

	Number of Cases	Mean (Gm/100cc)	Standard Deviation (±)	Significance (P)*
Pulmonary Tbc., Active	135	0.2	0.15	P > 0.5
Pulmonary Tbc., Inactive	34	0.26	0.11	P > 0.5
Chronic Bronchitis	14	0.28	0.13	P > 0.9
Bronchiectasis	12	0.24	0.11	P > 0.4
Bronchial Asthma (Inf.)	10	0.26	0.14	P > 0.7
Bronchial Asthma (Allergic)	20	0.28	0.13	P > 0.9
Bronchial Asthma (Mixed)	29	0.24	0.09	P > 0.2
Controls	41	0.28	0.1	-------
	295			

* P value < 0.05 shows a significant difference between the groups compared.

TABLE V

THE SERUM ALPHA-2 GLOBULIN LEVEL IN EACH GROUP AS COMPARED TO THE CONTROL GROUP

	Number of Cases	Mean (Gm/100cc)	Standard Deviation (±)	Significance (P)*
Pulmonary Tbc., Active	135	0.79	0.27	P > 0.4
Pulmonary Tbc., Inactive	34	0.73	0.23	P > 0.9
Chronic Bronchitis	14	0.95	0.40	P > 0.2
Bronchiectasis	12	0.78	0.34	P > 0.7
Bronchial Asthma (Inf.)	10	0.73	0.33	P > 0.9
Bronchial Asthma (Allergic)	20	0.83	0.41	P > 0.5
Bronchial Asthma (Mixed)	29	0.75	0.24	P > 0.8
Controls	41	0.73	0.41	-------
	295			

* P value < 0.05 shows a significant difference between the groups compared.

TABLE VI

THE SERUM BETA GLOBULIN LEVEL IN EACH GROUP
AS COMPARED TO THE CONTROL GROUP

	Number of Cases	Mean (Gm/100cc)	Standard Deviation (±)	Significance (P)*
Pulmonary Tbc., Active	135	0.96	0.34	P > 0.4
Pulmonary Tbc., Inactive	34	1.10	0.37	P > 0.6
Chronic Bronchitis	14	1.06	0.38	P > 0.9
Bronchiectasis	12	1.00	0.49	P > 0.8
Bronchial Asthma (Inf.)	10	1.09	0.44	P > 0.7
Bronchial Asthma (Allergic)	20	1.03	0.41	P > 0.9
Bronchial Asthma (Mixed)	29	0.98	0.34	P > 0.6
Controls	41	1.04	0.35	-------
	295			

* P value < 0.05 shows a significant difference between the groups compared.

TABLE VII

THE SERUM GAMMA GLOBULIN LEVEL IN EACH GROUP,
AS COMPARED TO THE CONTROL GROUP

	Number of Cases	Mean (Gm/100cc)	Standard Deviation (±)	Significance (P)*
Pulmonary Tbc., Active	135	1.57	0.56	$P < 0.02$
Pulmonary Tbc., Inactive	34	1.62	0.41	$P < 0.01$
Chronic Bronchitis	14	1.68	0.66	$P < 0.02$
Bronchiectasis	12	1.94	0.68	$P < 0.001$
Bronchial Asthma (Inf.)	10	1.70	0.42	$P < 0.01$
Bronchial Asthma (Allergic)	20	1.32	0.33	No significant difference
Bronchial Asthma (Mixed)	29	1.26	0.40	No significant difference
Controls	41	1.33	0.37	--------
	295			

* P value < 0.05 shows a significant difference between the groups compared.

REVIEW OF LITERATURE

Seibert and Nelson in 1942 were among the first to report serum electrophoretic changes in cases of pulmonary tuberculosis. (10) They observed that the elevated gamma globulin level in minimal tuberculosis increased as the extent of involvement increased. In far-advanced tuberculosis, they noted an increase in all the globulin fractions. In 1943, the same authors compared the serum protein changes observed in human tuberculosis with those observed in rabbits with experimentally induced tuberculosis. (11) Sera obtained from the rabbits showed a constant decrease in albumin and an increase in beta globulin fractions; whereas the human sera revealed a decrease in albumin and an increase in alpha and gamma globulin concentrations.

In a separate study, Seibert and others reported an increase in the true polysaccharide content of the serum in human tuberculosis. (12) The level of this polysaccharide was, to some extent, proportionate to the degree of involvement.

Seibert and associates in 1947 correlated the serum protein patterns with the extent of tuberculous involvement. In minimally-active tuberculosis, they reported a rise in the level of gamma globulin fraction and a fall in albumin fraction; in moderately-advanced tuberculosis they observed, in addition to the above changes, an increase in the alpha-2 globulin fraction. They related the rise in the latter fraction to the increased polysaccharide content of the serum. In

far-advanced pulmonary tuberculosis they described an increase in all the globulin fractions along with a decrease in the albumin concentration. There was, however, no change in the mean total protein. The increase in gamma globulin in minimal tuberculosis was attributed to antibody formation, whereas the simultaneous rise in alpha-2 globulin and polysaccharide in advanced tuberculosis probably represented tissue destruction.

In 1948, Seibert et al. described a simple method for determining the presence of a polysaccharide-like substance in the serum. (14) The test was based on a reaction between the tryptophan and the carbohydrate complex. A significant rise of the level of this polysaccharide-like substance, the exact nature of which is unknown, was found in cases of tuberculosis.

Mertens and Bunge in 1950 noted an increase in the serum level of alpha globulins in exudative tuberculous processes, while a marked rise was noted in the coarsely-dispersed globulins (fibrinogen and gamma globulin) in the chronic, proliferating, and cirrhotic forms. (15) They related a significant increase of the alpha globulin to a progression of the disease. On the other hand, a marked increase of the coarsely-dispersed proteins, especially gamma globulin, suggested a good defense by the host.

Using the Kunkel method (16), Small in 1950 studied the gamma globulin contents of serum in a series of 150 tuberculous patients. (17) He failed to confirm Seibert's earlier findings that an increase in gamma globulin content usually kept pace with the progress of the disease. Instead, he felt that there was considerable overlapping of values in the minimal, moderately-, and far-advanced active cases.

According to Small, the hepatotoxic changes described by Mertens and Bunge could be related to the use of an antituberculosis drug called contaben.

In 1953, Schaffner et al. correlated the serum levels of gamma globulin, mucoproteins, and polysaccharides with the histological changes found in liver and lymph node biopsy and sternal marrow specimens in twenty-three patients with far-advanced pulmonary tuberculosis. (18) A statistically significant correlation was found between the level of the serum gamma globulin, total degree of hepatic alteration, and the number of plasma cells in the bone marrow. In their opinion, the level of serum gamma globulin reflected the severity of the nonspecific host reactions seen in the liver.

Volk and associates in 1953 observed that all patients with active pulmonary tuberculosis, including those with minimal lesions, showed some increase of the gamma globulin. (19) They thought that the severity of the disease, as well as the prognosis, could be correlated with the changes in the gamma globulin level. The alpha-2 and beta globulin levels were not valid prognostic indicators because they remained elevated,even in the arrested cases. Serial electrophoretic determinations were recommended to monitor the gamma globulin changes.

Baldwin and Iland in 1953 reported an increase in alpha-1, alpha-2, and gamma globulin fractions as the tuberculous process progressed. (20) These changes were accompanied by a corresponding decrease in the albumin concentration of the serum. The same pattern was observed in cases of bone and renal tuberculosis. They also demonstrated a complement-fixing antibody in the gamma globulin fraction of the sera of some patients with advanced pulmonary tuberculosis. When the

tuberculous serum was absorbed with Mycobacterium tuberculosis, no changes were observed in the concentration of this fraction. They concluded that increased antibody production was not responsible for the rise in gamma globulin.

Kanagami in 1954 studied serum proteins of 122 patients with pulmonary tuberculosis who had had no prior chemotherapeutic treatment. (21) Although he observed no correlation between the beta globulin and the disease process, he was able to confirm the other serum changes, that is, increases in alpha-1, alpha-2, and gamma globulins.

Saifer et al. in 1954 studied patients who were undergoing isoniazid therapy, and reported that their serum protein patterns reflected the clinical course of the disease. (22) They concluded that this technique could be used to evaluate objectively the changing status of the tuberculous process.

Matsui and Tamura in 1955 confirmed the correlation of decreased albumin with the severity of the disease process. (23) The decrease in the beta globulin fraction was greater in the cases of far-advanced tuberculosis than in the moderately-advanced cases.

Vannini, Mulargia, and Gelli in 1955 observed a decrease in serum albumin and an increase in alpha and gamma globulins in the patients subjected to thoracoplasty or extrapleural pneumothorax. (24) In the same year, Meyer and co-workers showed that changes in the alpha-2 globulin level could be correlated with the patient's status--increasing with progression of disease and decreasing with improvement. (25) They regarded a persistence or reappearance of an increase of alpha-2 globulin as of serious prognostic significance.

In a study involving 327 patients suffering from pulmonary tuberculosis and 28 unaffected "contacts" used as controls, Gilliland and associates in 1956 observed higher alpha-2 globulin concentrations in the tuberculous group.(26) They thought that the albumin/alpha-2 ratio was a more sensitive index of tuberculous activity than the erythrocyte sedimentation rate. The observations of Gilliland and many previous workers were further confirmed by Rawlings et al. in 1956. (27)

Jencks and co-workers in 1956 studied the serum electrophoretic patterns of more than 1500 patients admitted to an army general hospital. (28) According to them, abnormalities of serum protein distribution were most frequently associated with infections (particularly tuberculosis), malignant neoplasms, arteriosclerosis, rheumatic heart disease, hepatitis, cirrhosis, rheumatoid arthritis, and sarcoidosis. Jencks usually noted a decrease in serum albumin, which was followed by an elevation of alpha-1, alpha-2, beta and gamma globulins; a rise in the level of albumin and a decrease in the serum globulin was observed only rarely.

McCuiston and Hudgins in 1960 reported that the serum electrophoretic changes observed in 74 cases of pulmonary diseases caused by unclassified Mycobacteria (nonphotochromogenic) resembled those observed in sarcoidosis. (29) There was a decrease in serum albumin, and an increase in gamma globulin without a concomitant rise in alpha-2 globulin.

Chievitz and Thiede in 1960 used the serum electrophoretic technique to differentiate pulmonary tuberculosis from other wide-spread pulmonary diseases. (30) In their opinion, low serum albumin and high

alpha-2 and gamma globulins indicate tuberculosis; however, the comination of low albumin and low gamma globulin tends to exclude the diagnosis, even when the alpha-2 globulin is elevated.

In asthma almost all of the studies of serum proteins have been done with children. Usually the studies are concerned with the empirical value of the use of gamma globulin in the treatment of asthma associated with repeated respiratory infections. Cooke and others in 1951 were among the first to study the serum protein patterns in adult patients with chronic asthma. (31) They found that four out of nineteen patients had an essentially normal albumin/globulin ratio, while the remaining fifteen had a hyperglobulinemia which coincided with a lowered albumin/globulin ratio. The serum gamma globulin concentration was definitely above normal values in four instances, and slightly elevated in several others. Elevation of alpha globulin was distinct in eight patients, and slightly so in several others. The beta globulin values in twelve patients were within normal range; however, the remaining six subjects exhibited a somewhat lower value. In one instance, alpha-2 and beta globulins failed to separate during the electrophoresis. The sera of the two adult patients whose chronic asthma was due entirely to extrinsic causes showed a normal albumin/globulin ratio. According to these workers, the changes found in the serum proteins were not the product of the allergic state per se. Since similar alterations of protein distribution were found in nonallergic infections such as osteomyelitis and bronchiectasis, these changes appeared to be related directly or indirectly to the chronic underlying infection.

Rose and associates in 1956 studied the serum proteins in a number of different diseases, including asthma, urticaria, periarteritis nodosa, penicillin reactions, serum sickness, erythema nodosum, and lupus erythematosus disseminatus. (32) They found nothing of any consequence in the clear-cut cases of allergy: the changes in serum proteins, if any, were entirely nonspecific. (33)

Ferri et. al. in 1956 used the paper electrophoretic technique to study 44 samples of sera from 41 asthmatic patients and 38 specimens from nonasthmatic individuals. (34) The asthmatic patients were divided into three groups--allergic, infectious, and mixed-type. Statistical analysis of the average values for each protein fraction revealed a decrease in albumin, increase in alpha-2 and gamma globulin, and no significant difference between average values of beta and alpha-1 globulins.

Tuft in 1956 reported that serum paper electrophoresis examinations of 121 children showed lowered albumin and an elevated alpha-2 and gamma globulin. (35) Patients who did not have an acute asthmatic episode for at least 31 days showed changes limited to the albumin and gamma globulin fractions. Steroid therapy had these effects on the electrophoretic pattern: an increase in the albumin and alpha-1 globulin levels; no effect on the previously elevated alpha-2 globulin; and a decrease in the gamma globulin levels toward normal.

In 1958 Stroh and Eriksen reviewed the serum protein patterns on 54 patients (adults and children) with a history of infection or suffering from either asthma or other allergic conditions. (36) These patterns were compared with those obtained from 22 healthy individuals of comparable ages. The patients frequently showed an increase in

alpha-1 and alpha-2 globulins and a decrease in albumin. These changes appeared to be associated with infections and other general pathologic processes, rather than allergic disorder per se. Although changes in beta and gamma globulin were occasionally observed, they were not statistically significant. Stroh and Eriksen confirmed the findings of Cooke et al. that serum protein electrophoretic changes ordinarily were not specific in allergic diseases.

Dees and Grunt in 1960 found no characteristic serum protein changes in a controlled study involving 283 allergic children. (37) Again, their conclusions were similar to those of Cooke et al., and Stroh and Eriksen.

Vaccarezza in 1960 studied serum electrophoretic patterns of forty patients with respiratory allergies. (38) Thirty patients of this group were considered to be the purely allergic type; ten patients had superimposed sinal or bronchial infection. In the purely allergic patients, there were no statistically significant changes in the serum albumin pattern. A nonsignificant diminution of the albumin level was found in 40 per cent of the cases in the infected group. There was a marked and constant rise of the alpha-1 globulin in both the purely allergic and the infectious groups. The beta globulin was found to have increased in 46 per cent of purely allergic patients and 70 per cent of the infected group. In both instances, statistical analysis showed that the changes were highly significant. There was no noticeable change in the gamma globulin in the purely allergic patients, but a 40 per cent increase was observed in the infectious group of asthmatics.

No attempt will be made to review in detail the voluminous literature discussing the use of serum electrophoretic techniques in the various diseases. Gutman has summarized almost all of the important findings in a review of the results obtained with the moving boundary method. (39) Other studies include Luetscher (40) and Fisher (41) (reviews); Lever (42) (emphasizes dermatologic conditions); Flynn (43) (qualitative estimation of abnormalities in paper electrophoretic patterns); Koiw et al. (44), Paton et al. (45), and Macheboeuf et al. (46) (paper electrophoresis); Coryell et al. (47) (pregnancy); Arends et al. (48) (Hodgkin's disease and lymphoma); Rundles et al. (49) (leukemia); Ropes et al. (50) and Hunt (51) (rheumatoid arthritis); Squire (52), Fisher et al. (53), and Stickler et al. (54) (nephrotic syndrome); Mahaux and Koiw (55) (myxedema); Bruton (56) (agammaglobulinemia); Osserman and Lawlor (57) (multiple myeloma); Wilson and Lubschez (58) (rheumatic fever); Satoskar et al. (59) (hepatitis); Stauber (60) (parasitology); and Kay (61) (paper electrophoresis in the differential diagnosis of ascites).

Finally, Ogryzlo et al. studied one hundred normal subjects as well as patients with a wide variety of diseases. (62) They observed that in the normal subjects,the total quantity of the serum proteins and the concentration of the various globulin components usually remain fairly constant within a relatively narrow range. Significant deviations from the normal values have not been consistent with continued good health. As mentioned earlier, the most common change in the serum proteins during the course of various diseases is the reversal of albumin/globulin ratio. Hyperglobulinemia associated with hypergammaglobulinemia may be observed in a variety of diseases. Table VIII,

derived from the article by Gross et al. (63), shows the various conditions in which hypergammaglobulinemia has been noted.

TABLE VIII

CONDITIONS IN WHICH HYPERGAMMAGLOBULINEMIA HAS BEEN NOTED*

I. INFECTIONS
- A. Bacterial
  1. Streptococcal, especially in subacute bacterial endocarditis, rheumatic fever and acute glomerulonephritis
  2. Severe staphylococcal infections
  3. Advanced tuberculosis, pulmonary and extrapulmonary
  4. Lepromatous leprosy
- B. Spirochetal
  1. Syphilis (all 3 stages)
- C. Viral
  1. Lymphogranuloma venereum**
  2. Infectious mononucleosis
  3. Psittacosis
- D. Rickettsial
  1. Typhus
- E. Fungal
  1. Histoplasmosis
- F. Protozoal
  1. Kala-azar**
  2. American mucocutaneous leishmaniasis
  3. Malaria
- G. Helminthic
  1. Visceral larva migrans (toxicara canis or catis)**
  2. Trichinosis
- H. Chronic infection** of nonspecific etiology

II. HYPERIMMUNIZATION**

III. LIVER DISEASE
- A. Portal cirrhosis**
  1. Laënnec's cirrhosis
  2. Postnecrotic cirrhosis
- B. Acute viral hepatitis
- C. Toxic hepatitis (such as that from arsenic)
- D. Chronic liver disease in young women with extreme hypergammaglobulinemia ("lupoid hepatitis")**
- E. Cholangiolitic hepatitis
- F. Biliary cirrhosis (late)

IV. SEVERE MALNUTRITION
- A. Kwashiorkor
- B. Nutritional-recovery syndrome**

V. NEOPLASMS
- A. Multiple myeloma**
- B. Leukemia (monocytic, chronic myelogenous and chronic lymphatic)

TABLE VIII (Cont'd)

C. Lymphomas
   1. Hodgkin's disease
   2. Lymphosarcoma
   3. Reticulum-cell sarcoma
D. Primary carcinoma and sarcoma, with or without metastases

VI. PARAPROTEINEMIAS AND DYSPROTEINEMIAS
   A. Macroglobulinemia**
   B. Cryoglobulinemia**
   C. Benign hyperglobulinemic purpura**
   D. Amyloidosis

VII. DISEASES POSSIBLY ASSOCIATED WITH HYPERSENSITIVITY
   A. Connective-tissue diseases ("collagen" diseases)
      1. Disseminated lupus erythematosus**
      2. Scleroderma**
      3. Rheumatic fever
      4. Rheumatoid arthritis
      5. Ankylosing spondylitis
      6. Periarteritis nodosa
      7. Sjögren's syndrome
   B. Others
      1. Serum sickness
      2. Acquired immune hemolytic anemia
      3. Autoimmune thyroiditis; Hashimoto's disease
      4. Erythema nodosum

VIII. GRANULOMAS
   A. Sarcoidosis**
   B. Chronic beryllium poisoning

IX. DERMATOLOGIC DISORDERS
   A. Pemphigus vulgaris (late)
   B. Extensive dermatitis (such as exfoliative dermatitis)
   C. Burns

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* Gross, P.A.M. et al., New Engl. J. Med., 260:121-125, 1959.

** Often associated with striking elevations of gamma-globulin fraction.

DISCUSSION

Changes in the serum proteins may be seen in many diseases. In most instances, there is a decrease in albumin concentration and an increase in the globulins. This disturbance in the serum proteins is generally known as alteration in the A/G ratio; the standards usually accepted are those determined by the chemical precipitation technique.

Infection is one of the most important conditions giving rise to increased serum globulin levels. Initially, acute infections may cause a rise in the alpha globulin and a fall in the serum albumin. (64) If the infection persists or produces a local lesion (abscess or endocarditic focus), the rise in the gamma globulin level occurs following the absorption of the antigenic and breakdown products. (63)

This view is supported by the findings presented in this study. High gamma globulin levels were recorded in the cases of active and inactive pulmonary tuberculosis, chronic bronchitis, bronchiectasis, and asthma associated with repeated respiratory infections. Gamma globulin levels were within normal limits in two groups of patients, namely, those who had only allergic asthma and the so-called "mixed asthma" which had both infectious and allergic components.

It is important to realize, however, that these changes in gamma globulin levels are somewhat nonspecific. Similarly, in the chest diseases described, the increase of serum gamma globulin levels is nondiagnostic, and at best warns the observer that something is

wrong. A final diagnosis can be made only with the help of other laboratory aids and clinical judgment.

It is known that patients with agammaglobulinemia are unable to synthesize antibodies in response to specific antigens. In contrast, certain patients with multiple myeloma may not produce detectable antibodies following similar stress even though the gamma globulin (probably abnormal) may be present in normal or increased quantities. Although the quantitative measurements of gamma globulin in agammaglobulinemia and multiple myeloma are diametric opposites (absent in one and increased in the other), both conditions have in common a profound reduction in their antibody responses. (65)

Recently, Hammack et al. described four cases of repeated pneumococcal infections in which the serum electrophoretic patterns showed one or more discrete homogenous peaks characteristic of myeloma. (66) These patients also failed to produce an adequate response to typhoid antigen. On follow-up, one case died of plasma cell leukemia. Autopsy findings confirmed the diagnosis, but revealed no evidence of myeloma.

They studied four more such cases: one of these patients died of nocardia infection, and an autopsy showed multiple abscesses, particularly in the brain; another patient was found to have miliary tuberculosis at the time of autopsy. Originally, Hammack and others felt that the increased susceptibility of these patients to infection was limited only to those caused by the pneumococcus; later they noted a decreased host-resistance to other types of infections, including bacterial, tuberculous, and fungal. There was, however, no evidence of increased susceptibility to viral disorders. (67)

Smith studied thirteen individuals who did not have a myeloma but whose serum electrophoretic patterns were characterized by the presence of an abnormally well-defined globulin. (68) He applied the term "non-myelomatous paraproteinemia" to this disorder. Clinical and chemical studies were undertaken to assess the significance of such globulins. Some of these individuals were clinically well; others had diseases such as angina pectoris, tertiary syphilis, microcytic anemia, or chronic pulmonary infections. In some others an unusual incidence of chronic pulmonary diseases was associated with the presence of a macroglobulin or a cold precipitable globulin (cryoglobulin).

Owen and Rider also described four patients whose serum electrophoretic patterns showed discrete globulin peaks without any other evidence of myeloma. (69) Two of these patients had repeated episodes of pneumonia. Since all of these cases were unrelated to classic myeloma, Hammack and associates suggested a new term, "dysgammaglobulinemia syndrome." This term implies a disturbed function of the gamma globulin moiety, manifested clinically by repeated infections.

Since the quantitative measurement of gamma globulin offered no explanation for the increased susceptibility to infection an attempt was made by the present author to study the antibody response in some patients suffering from repeated respiratory infections. As tuberculosis and allergic asthma can be treated with specific therapy, the phase of the study herein described included only the patients suffering from a difficult-to-treat disease, chronic bronchitis.

Six patients with chronic bronchitis and histories in common

of repeated respiratory infections were selected for an immunological study. Three of these had elevated serum gamma globulin levels, and the remaining three had serum gamma globulin levels in the normal range. To these, three controls were added. All nine individuals were immunized, once each week for three weeks, with typhoid-paratyphoid vaccine. Agglutination tests, total proteins, and serum electrophoretic studies were done immediately before and three weeks after the course of immunization.

Table IX shows the data collected on the three controls. All three control subjects showed a good response in O and H agglutination titers.

The same finding was obtained in the three patients with chronic bronchitis and elevated gamma globulin levels. (Table X)

Of the three patients in the third group (with chronic bronchitis and normal gamma globulin levels), one patient failed to respond to both the H and O antigen. The second responded to the H antigen but not to the O antigen. The third patient gave a normal response. (Table XI)

In contrast with the results obtained by Hammack et al., the patients belonging to the second group (history of repeated respiratory infections and high gamma globulin levels) showed a fairly adequate antibody response to the typhoid antigen. However, one patient belonging to the third group (with chronic bronchitis but normal gamma globulin level) failed to respond to the typhoid antigen. Unfortunately, this patient could not be restudied before he left the hospital.

In cases of chronic lymphatic leukemia (70,71), Hodgkin's disease and other lymphomas (72,73), failure to produce circulating antibodies

has been suggested as a major weakness in the host's resistance to bacterial infection. Silver et al. compared the antibody responses to five antigens in ten patients with acute leukemia and in ten normal control subjects. (74) The use of five antigens was based on the assumption that there may be a significant difference in the degree of response to different antigens within the same individual. Table XII, as adapted from Silver et al., shows the results. Of the group of ten patients with leukemia, three responded to typhoid vaccine, two to mumps vaccine, and three to influenza vaccine. In contrast, seven control subjects responded to typhoid vaccine, seven to mumps vaccine, and eight to influenza vaccine. Of the ten patients with leukemia, seven responded with a significant rise after administration of diphtheria toxoid, in contrast to a rise in all ten of the control subjects. Six patients and seven normal subjects had significant titer rises after they had received tetanus toxoid. The response to any one antigen did not differ significantly in the two groups, and all but one of the patients with acute leukemia responded to at least one antigen. However, a significantly poorer response in the patients with acute leukemia could be demonstrated by comparing the over-all antibody response to all antigens of both groups.

It is possible that the over-all poor antibody response observed in the cases of lymphatic leukemia may also be present in cases of chronic bronchitis. The almost universal response to typhoid vaccine, as observed in the series of cases of chronic bronchitis described in this, the second phase of the study, suggested the use of more than one antigen, including both bacterial and viral materials.

Thus, eleven more patients with chronic bronchitis and varying

levels of serum gamma globulin were studied along with five control subjects. These individuals were challenged, during the third phase of the study, with multiple antigens--including diphtheria toxoid, staphage lysate, mumps, influenza, and typhoid-paratyphoid vaccines. The schedule for these injections is given in Appendix J. Blood samples were drawn in order to study the antibody titers immediately before and two weeks after the completion of injections. Unfortunately, the mumps and diphtheria sera were not stored properly and could not be used. Some of the sera for influenza happened to be anticomplementary and had to be discarded. The only samples that could be analyzed were those involving typhoid-paratyphoid, staphage lysate, and, to some extent, influenza vaccines. Although inconclusive, there did not appear to be any significant difference in the antibody responses of the three groups, namely, control, chronic bronchitis with high gamma globulin levels, and chronic bronchitis with normal gamma globulin levels. (Table XIII)

TABLE IX

AGGLUTININ TITERS IN SERA OF THREE CONTROLS BEFORE AND AFTER IMMUNIZATION WITH TYPHOID-PARATYPHOID VACCINE

Control	Gamma Globulin		Prior to Immunization 1:20	1:40	1:80	1:160	1:320	1:640	1:1280	Three Weeks after Immunization 1:20	1:40	1:80	1:160	1:320	1:640	1:1280
I.K.	1.1	O	++	+						++	++	++	+			
		H	++	++	++	+				++	++	++	++	++	+	
T.M.	1.6	O	++	++	++	++	+			++	+++	++	++	++	+	
		H	++	++	++	++	+			++	++	++	++	++	++	+
S.A.	0.92	O	++	++	+					++	++	++	++	++	+	
		H	++	++	+					++	++	++	++	++	+	

TABLE X

AGGLUTININ TITERS IN SERA OF THREE PATIENTS WITH CHRONIC BRONCHITIS (AND HIGH GAMMA GLOBULIN LEVELS) BEFORE AND AFTER IMMUNIZATION WITH TYPHOID-PARATYPHOID VACCINE

Patients	Gamma Globulin		Prior to Immunization							Three Weeks after Immunization					
			1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:20	1:40	1:80	1:160	1:320	1:640	1:1280
G.W.	2.2	O	--	--	--	--	--	--	--	++	+					
		H	--	--	--	--	--	--	--	++	++	++	++	++	+	
P.N.	2.3	O	--	--	--	--	--	--	--	++	++	+				
		H	--	--	--	--	--	--	--	++	+					
M.M.	2.1	O	--	--	--	--	--	--	--	++	++	++	++	+		
		H	--	--	--	--	--	--	--	++	++	+				

TABLE XI

AGGLUTININ TITERS IN SERA OF THREE PATIENTS WITH CHRONIC BRONCHITIS (AND NORMAL GAMMA GLOBULIN LEVELS) BEFORE AND AFTER IMMUNIZATION WITH TYPHOID-PARATYPHOID VACCINE

Patients	Gamma Globulin		Prior to Immunization							Three Weeks after Immunization						
			1:20	1:40	1:80	1:160	1:320	1:640	1:1280	1:20	1:40	1:80	1:160	1:320	1:640	1:1280
C.B.	0.85	O	--	--	--	--	--	--	--	--	--	--	--	--	--	--
		H	--	--	--	--	--	--	--	--	--	--	--	--	--	--
B.M	1.3	O	--	--	--	--	--	--	--	--	--	--	--	--	--	--
		H	--	--	--	--	--	--	--	++	++	+				
M.M.	1.1	O	--	--	--	--	--	--	--	++	++	++	++	+		
		H	++	++	++	+				++	++	++	++	++	+	

TABLE XII

FOURFOLD OR GREATER RISE ON DAY 26 IN PATIENTS WITH LEUKEMIA AND IN NORMAL SUBJECTS

Subj. No.	Typhoid H	Mumps	Influenza	Diphtheria	Tetanus	Individual Score
Pts.						
1	0	0	0	+	+	2
2	0	0	0	0	0	0
3	0	0	0	0	+	1
4	0	+	+	+	+	4
5	0	0	0	+	+	2
6	+	+	0	+	+	4
7	0	0	+	+	+	3
8	+	0	0	0	0	1
9	+	0	+	+	0	3
10	0	0	0	+	0	1
Totals	3	2	3	7	6	21
Control Subjs.						
11	+	+	+	+	+	5
12	+	+	+	+	+	5
13	+	+	+	+	+	5
14	+	0	+	+	0	3
15	+	0	+	+	0	3
16	+	+	0	+	0	3
17	+	+	0	+	+	4
18	0	0	+	+	+	3
19	0	+	+	+	+	4
20	0	+	+	+	+	4
Totals	7	7	8	10	7	39

Adapted from: Silver, R.T. et al., J. Lab. Clin. Med., 56:638, 1960.

TABLE XIII

ANTIBODY TITERS IN SERA OF ELEVEN PATIENTS WITH CHRONIC BRONCHITIS AND FIVE CONTROLS, BEFORE AND AFTER IMMUNIZATION WITH VARIOUS ANTIGENS

Subject	Gamma Glob. Gm/100 ml	Expressed as reciprocal of highest serum dilution. Typhoid* H	Typhoid* O	Staphage-lysate**	Influenza***
Control Subjs.		Before-After	Before-After	Before-After	Before-After
S.A.	1.29	40 - 40	160 - 160	1600 - 800	16 - 16
I.K.	0.95	80 - 80	160 - 160	400 - 1600	8 - 16
E.K.	1.34	40 - 40	160 - 640	1600 - 1600	AC - AC
W.D.	0.75	10 - 80	<10 - 40	800 - 1600	AC - 8
A.M.	0.76	<10 - 80	40 - 160	200 - 400	Not done
Patients					
J.D.	1.67	<10 - 640	80 - 160	1600 - 1600	64 - 128
D.D.	1.62	<10 - 80	40 - 160	1600 - 1600	16 - 32
F.A.	2.46	<10 - 40	10 - 20	3200 - 1600	8 - 8
M.W.	1.95	20 - 80	160 - 320	1600 - 1600	Not done
W.F.	0.58	<10 - <10	10 - 40	400 - 800	Not done
O.K.	0.81	<10 - 40	20 - 40	800 - 800	8 - 64
I.E.	0.96	<10 - <10	20 - 40	800 - 1600	Not done
G.K.	1.03	10 - 40	20 - 1280	800 - 800	AC - AC
E.V.	0.76	<10 - 10	160 - 320	800 - 1600	Not done
A.S.	0.81	80 - 40	160 - 160	800 - 800	Not done
L.P.	1.29	<10 - 40	160 - 160	1600 - 800	AC - AC

AC = anti-complementary.

* Lederle Laboratories, N. Y., Diagnostic Agents for Clinical and Laboratory Use, p. 35.

** Boger, W.P., Frankel, J.W., and Gavin, J.J. Detection and titration of staphylococcus aureus agglutinin in serum. Proc. Soc. Exp. Biol. and Med., 104:639, 1960.

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SUMMARY AND CONCLUSIONS

In the first part of this study, the serum electrophoretic patterns were observed in 295 adults. They were divided into eight groups: Active pulmonary tuberculosis, 135; inactive pulmonary tuberculosis, 34; chronic bronchitis, 14; bronchiectasis, 12; infectious asthma, 10; allergic asthma, 20; and mixed-type asthma, 29. Forty-one subjects with no histories of known chest disease and with normal chest x-ray films were used as controls. The T-test for unpaired variates was used to evaluate the difference between each of the seven disease groups and the control group.

A statistically significant decrease of serum total proteins was observed in the cases of mixed-type bronchial asthma when this group was compared with the control group. There was a borderline decrease of serum total proteins in the patients with chronic bronchitis. No significant changes were noted in patients belonging to the other groups studied.

When compared with the control group, there was a significant reduction of serum albumin in cases of active and inactive pulmonary tuberculosis and chronic bronchitis, a borderline reduction in cases of bronchiectasis and bronchial asthma of the mixed type, and no significant difference in cases of bronchial asthma of the allergic and infectious types.

No significant changes were noted in alpha-1, alpha-2, and beta globulin levels in any of the groups when comparison was made with

the control group.

There was a marked rise in the level of gamma globulin in the cases of bronchiectasis; a significant rise in gamma globulin levels in the cases of active and inactive pulmonary tuberculosis, chronic bronchitis, and asthma of infectious origin. Allergic and mixed-type asthma cases had no significant changes in gamma globulin levels.

Another series of six patients with chronic bronchitis (a group of three with normal gamma globulin levels, and a second group of three with high levels) and three controls were inoculated with typhoid-paratyphoid vaccine in order to learn their antibody response. Of the group with normal gamma globulin levels and chronic bronchitis, one patient failed to give any response at all, either to H or O antigen; the second gave a good response to H antigen, but no response to O antigen; and the third patient responded normally. The control group and the three patients with chronic bronchitis with high gamma globulin levels also responded adequately to the typhoid antigen.

Since an individual may respond normally to one antigen and poorly to another, it is necessary to study a subject's response to several antigens before making any decisions about the individual's antibody response. With this in mind, multiple antigens were given to another group of eleven patients with chronic bronchitis, and to five control subjects. Although the results were somewhat inconclusive because of certain technical difficulties, none of these individuals appeared to display any significant abnormality in his antibody response.

On the basis of this study, the following conclusions may be put forth: 1) Different chest diseases which are associated with

chronic infections may be accompanied by gamma globulin levels higher than normal. However, this rise in the level is nondiagnostic and nonspecific. 2) Lack of antibody response does not seem to be of major importance in chronic bronchitis patients having histories of repeated respiratory infections.

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APPENDIX

APPENDIX A

THE CONCENTRATIONS OF SERUM PROTEIN FRACTIONS (GM/100cc) IN 135 CASES OF ACTIVE PULMONARY TUBERCULOSIS

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	M.L.	F	25	7.0	3.33	0.17	0.55	0.59	1.49
2	C.M.	F	17	8.4	3.16	0.38	1.08	2.01	1.76
3	J.M.	M	24	7.7	5.70	0.15	0.52	0.68	0.55
4	M.R.	F	22	7.2	4.76	0.20	0.57	0.86	0.66
5	H.S.	F	50	7.7	4.16	0.18	0.63	1.47	1.10
6	S.C.	M	30	7.7	5.20	0.23	0.42	0.81	1.08
7	M.H.	F	39	6.9	3.75	0.19	0.56	0.68	1.70
8	A.P.	F	49	8.1	4.34	0.24	0.58	0.83	1.94
9	S.M.	M	19	6.6	3.07	0.29	1.14	1.25	0.48
10	M.R.	F	18	8.2	3.47	0.39	1.34	1.23	1.77
11	B.B.	M	51	8.5	4.68	0.15	0.85	0.21	2.55
12	N.L.	F	28	7.0	4.43	0.25	0.50	0.76	1.06
13	M.L.	F	48	7.8	5.18	0.18	0.38	0.84	1.00
14	M.L.	F	63	8.5	6.02	0.26	0.67	0.85	0.67
15	M.L.	F	53	6.6	4.53	0.18	0.69	0.50	0.55
16	E.M.	F	18	7.3	3.87	0.22	0.48	1.00	1.68
17	R.M.	M	39	7.4	4.82	0.21	0.54	0.98	0.83
18	W.N.	M	55	6.7	3.10	0.18	0.74	1.02	1.70
19	F.N.	M	44	6.6	3.33	0.27	1.03	1.10	0.86
20	R.O.	M	30	7.9	4.51	0.13	0.44	0.81	2.09
21	S.P.	F	78	6.5	2.18	0.39	0.81	1.11	2.07
22	M.P.	F	46	6.7	2.93	0.28	1.13	1.21	1.05
23	E.P.	F	23	7.9	3.80	0.27	0.88	0.98	1.86
24	J.R.	M	46	8.3	3.91	0.37	1.10	1.38	1.52
25	L.R.	F	36	10.5	6.65	0.43	0.99	0.86	1.61
26	J.R.	F	25	7.4	3.53	0.24	0.73	0.84	2.05
27	M.S.	F	46	8.5	5.85	0.17	0.55	0.55	1.31
28	M.S.	F	34	7.1	3.55	0.23	0.72	0.72	1.57
29	J.S.	M	46	7.8	4.13	0.22	1.04	1.40	1.04
30	H.S.	F	45	7.3	2.72	0.39	0.78	0.68	2.75
31	L.T.	M	37	8.2	3.79	0.34	0.61	1.62	1.82
32	H.U.	M	62	7.2	3.24	0.21	0.67	0.91	2.33
33	A.V.	F	47	7.0	4.21	0.16	0.31	0.62	1.52
34	L.W.	M	21	7.7	3.31	0.85	1.20	0.25	2.69
35	C.W.	M	28	6.2	3.08	0.27	0.70	0.77	1.34
36	J.Y.	M	32	7.6	4.10	0.36	0.82	0.85	1.39
37	D.M.	F	63	7.3	4.23	0.44	0.80	1.10	1.53
38	M.S.	F	49	6.3	2.87	0.34	0.60	1.11	1.37
39	N.F.	F	63	7.0	3.29	0.31	0.70	0.70	1.96
40	J.M.	F	35	7.2	3.74	0.14	0.52	0.32	1.91
41	W.A.	M	55	7.2	2.56	0.41	1.27	1.01	1.77
42	L.A.	F	40	6.6	2.47	0.23	0.61	1.12	1.43
43	M.A.	F	58	7.9	3.79	0.31	0.94	1.22	1.49

Appendix A: The Concentrations of Serum Protein Fractions (GM/100cc) in 135 Cases of Active Pulmonary Tuberculosis (Cont'd)

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
44	J.A.	F	35	7.26	3.78	0.15	0.52	0.83	1.92
45	R.B.	M	43	7.10	4.47	0.21	0.43	0.87	1.08
46	F.B.	M	59	4.4	1.40	0.29	1.11	1.03	0.55
47	I.B.	F	28	9.9	4.69	0.27	0.97	1.41	2.43
48	C.B.	M	42	7.8	3.97	0.28	0.96	0.87	1.70
49	E.B.	F	29	7.92	3.92	0.22	0.90	0.90	1.85
50	I.C.	F	23	7.50	2.88	0.30	1.14	1.38	1.80
51	H.C.	F	33	7.60	5.40	0.03	0.37	0.65	1.10
52	J.C.	M	26	7.40	4.37	0.23	0.52	0.61	0.61
53	G.C.	F	56	8.9	4.69	0.31	0.56	0.89	2.40
54	E.C.	M	22	6.8	4.25	0.12	0.44	0.75	1.0
55	J.C.	M	20	8.1	4.37	0.27	1.02	0.93	1.78
56	M.D.	M	51	7.8	4.13	0.21	0.97	0.92	1.47
57	R.D.	M	20	7.91	4.14	0.36	0.55	0.91	1.87
58	G.D.	F	43	7.4	4.63	0.20	0.47	0.72	0.87
59	J.F.	M	35	7.5	4.43	0.23	0.59	0.86	1.26
60	W.G.	M	20	7.4	3.69	0.41	1.07	1.15	0.98
61	D.G.	F	55	6.5	3.28	0.21	0/87	0.73	1.28
62	R.H.	M	43	7.1	4.27	0.31	0.83	0.65	1.04
63	B.H.	M	49	7.4	3.57	0.38	1.07	1.00	1.30
64	W.J.	M	48	8.0	3.79	0.18	0.71	1.13	2.06
65	H.J.	F	24	8.3	4.37	0.23	0.89	0.92	1.88
66	P.J.	F	22	7.9	3.71	0.28	1.62	0.88	1.33
67	M.K.	M	22	7.3	5.28	0.09	0.39	0.41	1.13
68	J.A.	M	45	7.3	3.83	0.12	0.95	1.10	1.37
69	W.A.	M	54	7.4	3.47	0.40	0.87	1.07	1.40
70	M.B.	F	44	8.6	2.97	0.33	1.48	1.64	2.18
71	P.B.	M	61	7.3	3.53	0.27	0.72	0.83	1.91
72	D.B.	M	44	8.4	3.81	0.29	1.10	1.10	2.07
73	J.B.	M	43	7.6	2.86	0.34	0.98	1.82	1.59
74	E.B.	M	54	7.4	4.46	0.13	0.83	0.73	1.23
75	J.C.	M	52	6.9	3.71	0.27	0.58	0.61	1.66
76	J.C.	M	32	7.3	3.33	0.30	0.45	0.84	2.20
77	E.C.	F	32	7.7	4.97	0.23	0.62	0.77	1.12
78	W.D.	M.	53	8.2	3.79	0.34	1.09	1.15	1.84
79	R.D.	F	43	8.5	5.37	0.26	0.99	0.73	1.08
80	N.E.	M	51	5.7	2.18	0.26	0.92	0.63	1.65
81	W.E.	M	33	6.6	3.68	0.19	0.51	0.87	1.32
82	M.F.	F	30	7.4	3.69	0.29	0.58	0.83	1.95
83	J.F.	M	62	6.8	2.88	0.37	0.81	1.41	1.25
84	P.F.	F	31	6.9	3.21	0.24	0.72	0.79	1.90
85	K.G.	M	41	7.6	4.48	0.24	0.84	0.85	1.09
86	L.G.	M	48	7.99	3.50	0.36	0.16	2.36	1.61
87	E.G.	M	48	8.0	3.13	0.38	1.22	1.18	2.07
88	N.G.	M	54	7.2	2.82	0.59	1.07	1.30	1.43
89	N.G.	M	49	9.4	4.16	0.21	0.68	1.29	3.05
90	A.H.	M	48	8.7	4.44	0.29	1.21	1.38	1.42

Appendix A: The Concentrations of Serum Protein Fractions (GM/100cc) in 135 Cases of Active Pulmonary Tuberculosis (Cont'd)

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
91	J.H.	M	51	7.5	4.15	0.32	0.63	0.89	1.42
92	J.J.	M	60	8.7	3.78	0.42	1.02	0.77	2.70
93	E.J.	F	36	7.4	3.79	0.22	0.68	0.79	1.59
94	R.K.	M	27	7.4	3.71	0.37	0.98	1.39	0.92
95	A.K.	M	49	8.3	4.11	0.24	1.16	1.35	1.70
96	L.K.	M	50	7.8	4.59	0.21	0.50	0.93	1.44
97	D.L.	F	47	7.8	3.20	0.31	0.62	1.01	2.73
98	A.M.	F	60	6.6	3.22	0.24	0.97	1.03	1.06
99	M.M.	M	49	7.4	3.88	0.27	1.06	0.70	1.39
100	M.M.	F	34	8.1	3.13	0.41	1.11	1.53	1.84
101	H.M.	M	38	8.6	4.54	0.33	0.81	0.89	2.00
102	M.M.	M	48	6.3	1.52	0.23	0.93	0.52	3.04
103	M.M.	F	36	6.6	1.35	0.23	0.65	0.65	1.72
104	E.M.	F	41	7.7	2.53	0.44	0.85	1.16	2.53
105	J.M.	M	52	5.8	3.54	0.37	1.00	1.03	0.86
106	T.M.	M	40	7.2	3.96	0.4	0.68	0.89	1.45
107	C.N.	F	51	6.8	3.45	0.36	1.08	0.72	1.15
108	F.N.	F	49	7.1	2.84	0.28	0.81	0.97	2.02
109	D.P.	M	45	7.7	4.08	0.21	0.92	0.95	1.50
110	A.P.	F	33	7.4	4.32	0.17	0.75	0.85	1.32
111	M.P.	F	42	7.3	3.80	0.18	0.74	0.93	1.56
112	C.R.	M	57	7.3	3.30	0.39	1.14	1.11	1.28
113	O.R.	F	19	7.3	2.57	0.36	1.28	0.80	2.25
114	M.S.	F	41	7.1	4.86	0.19	0.42	0.65	0.96
115	E.S.	F	38	7.3	3.43	0.36	0.85	0.82	1.82
116	A.S.	M	52	7.6	4.38	0.11	0.80	1.38	0.80
117	H.S.	M	49	8.0	4.02	0.37	0.82	1.03	1.78
118	J.S.	M	54	7.5	3.18	0.29	0.59	0.62	2.82
119	E.S.	F	45	6.4	4.42	0.14	0.51	0.78	0.55
120	P.S.	F	40	7.2	4.18	0.19	0.58	0.87	1.32
121	A.S.	M	24	8.3	3.06	0.35	0.87	0.66	0.30
122	B.S.	F	41	7.7	2.86	0.36	0.85	1.10	2.45
123	I.T.	F	38	8.7	3.38	0.34	1.11	1.52	2.00
124	S.T.	M	29	7.6	5.27	0.25	0.38	0.71	1.04
125	R.T.	M	67	7.2	4.03	0.28	0.82	0.60	1.37
126	V.T.	M	31	7.1	3.93	0.22	0.55	0.94	1.30
127	J.T.	M	65	6.6	3.80		0.63	0.69	1.49
128	E.V.	M	56	8.6	3.71	0.20	0.72	1.73	2.21
129	M.Y.	F	31	7.3	3.50	0.30	0.72	0.96	1.74
130	M.C.	F	45	7.9	3.33	0.32	0.65	1.16	2.39
131	J.J.	M	32	7.2	3.28	0.22	0.57	1.04	1.99
132	C.B.	F	26	6.8	4.32	0.22	0.69	0.67	0.89
133	D.K.	F	30	7.15	4.75	0.29	0.44	0.56	1.11
134	J.H.	M	20	8.0	3.30	0.44	1.18	1.18	1.80
135	E.R.	F	29	7.7	3.97	0.22	0.62	1.11	1.77
	Mean			7.51	3.28	0.20	0.79	0.96	1.57

APPENDIX B

THE CONCENTRATION OF SERUM PROTEIN FRACTIONS (GM/100cc) IN 34 CASES OF INACTIVE PULMONARY TUBERCULOSIS

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	W.L.	M	68	6.7	3.48	0.23	0.78	1.01	1.21
2	P.R.	M	24	7.5	2.85	0.41	0.98	1.37	1.15
3	E.L.	F	33	8.1	3.54	0.26	0.88	1.25	2.10
4	M.D.	F	20	7.2	3.48	0.44	0.57	0.95	1.71
5	H.L.	F	33	6.75	3.14	0.20	1.07	1.11	1.23
6	J.Y.	F	24	7.2	2.87	0.40	0.96	1.43	1.53
7	L.W.	F	38	6.7	3.76	0.21	0.70	0.76	1.25
8	F.C.	F	30	8.4	5.09	0.21	0.43	1.11	1.54
9	T.E.	F	17	6.8	3.20	0.07	0.58	0.65	2.21
10	A.M.	M	33	8.0	4.55	0.38	0.61	0.56	1.90
11	W.S.	M	58	8.0	3.72	0.18	0.81	1.25	2.02
12	A.K.	F	27	6.9	3.73	0.32	0.75	0.77	1.26
13	D.M.	M	23	8.0	4.29	0.22	0.59	1.58	1.19
14	M.H.	F	46	7.0	3.61	0.20	0.57	1.01	1.61
15	S.K.	M	52	7.5	3.47	0.35	0.92	1.31	1.44
16	H.S.	M	27	6.8	3.65	0.24	0.54	0.79	1.58
17	J.O.	F	28	7.6	3.67	0.34	0.40	0.97	2.04
18	G.A.	M	17	8.0	3.40	0.24	1.02	1.70	1.64
19	W.B.	M	57	7.6	3.78	0.27	1.07	1.21	1.64
20	T.K.	M	37	7.7	3.57	0.14	1.00	1.35	1.64
21	M.D.	F	46	7.1	3.81	0.23	0.65	1.28	1.16
22	L.L.	F	34	6.9	3.55	0.19	0.53	0.82	1.74
23	R.S.	M	29	6.9	3.95	0.09	0.76	0.76	1.26
24	P.J.	F	25	7.2	3.78	0.22	0.78	0.78	1.63
25	D.C.	M	34	6.65	3.59	0.20	0.53	1.06	1.06
26	R.H.	F	40	6.70	3.30	0.24	0.72	1.13	1.31
27	T.C.	F	65	7.2	4.4	0.31	0.74	1.17	1.05
28	S.F.	M	54	7.8	3.2	0.55	0.45	1.15	2.45
29	G.H.	M	40	8.0	3.86	0.33	0.73	1.01	2.07
30	L.L.	M	49	7.6	2.35	0.27	0.87	1.72	1.85
31	A.S.	M	51	7.5	3.72	0.35	0.77	0.98	1.62
32	L.T.	F	39	7.0	3.72	0.27	0.90	0.62	1.43
33	J.E.	F	26	8.3	3.90	0.17	0.54	1.74	1.79
34	R.T.	M	43	8.0	3.55	0.13	0.74	0.80	2.85
	MEAN			7.39	3.63	0.26	0.73	1.10	1.62

APPENDIX C

THE CONCENTRATIONS OF SERUM PROTEIN FRACTIONS (GM/100ML.) IN 14 CASES OF CHRONIC BRONCHITIS

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	A.G.	M.	56	7.5	4.06	0.29	0.69	0.99	1.42
2	C.M.	F	57	5.9	3.33	0.11	0.68	1.01	0.74
3	D.P.	M	24	8.0	3.27	0.21	1.10	1.53	1.85
4	E.W.	F	64	5.8	2.51	0.23	0.53	0.73	1.78
5	D.C.	F	50	5.5	2.21	0.29	0.60	1.17	1.05
6	O.K.	F	26	6.8	3.07	0.39	1.45	0.78	1.03
7	N.M.	F	37	7.9	3.08	0.35	1.28	1.15	1.99
8	G.P.	M	52	7.0	3.07	0.42	1.07	0.94	1.49
9	P.N.	F	16	8.5	3.26	0.38	0.97	0.89	3.01
10	B.	M	56	6.6	3.00	0.13	0.69	0.74	1.68
11	D.M.	F	45	6.8	2.96	0.29	0.95	1.17	1.42
12	M.M.	F	15	8.8	3.26	0.36	1.37	1.21	2.61
13	C.B.	M	53	7.9	4.12	0.14	0.76	1.09	1.90
14	F.M.	M	57	6.7	2.33	0.33	1.13	1.39	1.50
	MEAN			7.12	3.11	0.28	0.95	1.06	1.68

APPENDIX D

THE CONCENTRATIONS OF SERUM PROTEIN FRACTIONS (GM/100ML.) IN 12 CASES OF BRONCHIECTASIS

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	G.B.	F	72	7.5	2.55	0.14	0.43	1.08	3.38
2	R.B.	M	61	6.9	2.77	0.19	1.45	0.94	1.50
3	M.B.	F	26	7.4	3.12	0.25	0.81	0.75	2.47
4	J.K.	M	70	8.0	4.29	0.32	0.90	1.34	1.31
5	B.R.	F	40	8.35	2.76	0.31	0.69	2.10	2.76
6	C.S.	M	42	7.6	3.38	0.35	0.82	0.74	2.25
7	G.S.	M	45	6.9	4.26	0.26	0.66	0.86	0.92
8	E.Z.	F	37	7.6	4.62	0.15	0.45	0.90	1.49
9	L.P.	F	48	6.1	1.93	0.32	1.00	0.90	1.67
10	M.B.	F	47	7.5	4.31	0.21	0.74	0.74	1.58
11	P.H.	M	47	7.0	3.02	0.31	0.92	0.78	1.97
12	O.S.	M	52	7.1	3.59	0.13	0.47	0.83	2.03
	MEAN			7.33	3.38	0.24	0.78	1.00	1.94

APPENDIX E

THE CONCENTRATIONS OF SERUM PROTEIN FRACTIONS (GM/100Ml.) IN 10 CASES OF INFECTIOUS ASTHMA

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	I.B.	F	52	8.5	3.51	0.40	1.10	1.19	2.38
2	W.B.	M	16	6.7	3.45	0.22	0.72	0.85	1.43
3	D.C.	M	43	8.0	4.55	0.20	0.59	1.04	1.58
4	E.C.	F	45	6.6	3.59	0.21	0.74	1.06	1.00
5	G.D.	F	47	7.8	3.92	0.25	0.55	1.12	1.97
6	P.S.	F	19	6.9	2.92	0.22	0.82	1.14	1.77
7	A.S.	F	47	7.5	3.65	0.10	0.38	1.65	1.63
8	J.V.	M	15	7.8	4.15	0.43	0.85	0.82	1.55
9	G.W.	F	27	6.8	2.28	0.38	0.98	0.87	2.28
10	D.A.	F	16	6.9	3.45	0.17	0.57	1.17	1.41
		MEAN		7.35	3.55	0.26	0.73	1.09	1.70

APPENDIX F

THE CONCENTRATIONS OF SERUM PROTEIN FRACTIONS (GM/100 ML) IN 20 CASES OF ALLERGIC ASTHMA

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	L.A.	M	26	8.0	4.66	0.14	0.61	0.94	1.74
2	J.A.	F	15	6.05	3.69	0.16	0.53	0.48	1.19
3	P.B.	F	18	7.95	3.64	0.39	1.28	1.40	1.24
4	A.B.	M	18	7.64	3.91	0.11	1.19	1.07	1.51
5	A.B.	F	19	7.90	4.19	0.19	0.95	0.87	1.54
6	L.B.	F	16	7.26	3.53	0.20	1.08	1.08	1.32
7	L.B.	F	36	8.25	3.76	0.54	0.27	1.54	2.18
8	J.C.	M	16	7.10	4.57	0.23	0.67	0.61	1.02
9	A.C.	M	17	7.35	5.15	0.22	0.54	0.46	0.99
10	J.G.	F	20	7.2	3.76	0.29	0.96	1.06	1.11
11	B.G.	F	57	8.2	3.28	0.33	1.44	1.58	1.55
12	R.H.	M	35	8.6	4.37	0.21	0.90	1.46	1.55
13	J.K.	M	19	6.6	3.98	0.24	0.41	0.62	1.35
14	B.M.	M	38	6.9	3.57	0.41	0.56	1.17	1.17
15	J.M.	F	17	8.9	4.41	0.46	1.42	1.14	1.42
16	L.S.	M	19	6.60	3.47	0.35	0.63	1.16	1.00
17	F.S.	F	15	6.4	4.10	0.23	0.29	0.84	0.94
18	T.S.	M	18	6.2	3.91	0.19	0.61	0.76	0.71
19	H.S.	M	17	8.8	4.70	0.43	1.16	1.12	1.60
20	C.H.	F	15	7.10	3.02	0.32	1.18	1.33	1.28
		MEAN		7.45	3.98	0.28	0.83	1.03	1.32

APPENDIX G

THE CONCENTRATIONS OF SERUM PROTEIN FRACTIONS (GM/100 Ml) IN 29 CASES OF MIXED TYPE OF ASTHMA

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	B.A.	F	39	5.5	2.83	0.21	0.71	0.52	1.23
2	H.B.	M	61	7.1	4.15	0.25	0.80	0.58	1.29
3	M.C.	M	16	8.4	4.26	0.16	0.82	0.91	2.18
4	M.C.	F	28	7.1	4.18	0.24	0.77	9.77	1.01
5	H.F.	F	59	7.15	3.07	0.29	0.11	1.22	1.52
6	A.G.	F	52	7.9	3.79	0.28	0.85	1.42	1.47
7	R.G.	M	53	6.6	3.25	0.26	0.81	1.07	1.18
8	S.G.	F	52	6.2	3.50	0.30	0.86	0.92	0.61
9	S.G.	F	17	8.0	4.79	0.31	0.81	0.84	1.20
10	V.H.	F	47	6.3	3.79	0.14	0.86	0.74	0.66
11	M.H.	F	52	8.1	3.71	0.42	1.17	1.36	1.46
12	M.I.	F	18	7.1	3.52	0.20	0.99	1.33	1.06
13	M.L.	F	41	6.4	3.44	0.32	0.72	1.13	0.75
14	A.L.	M	55	6.9	3.86	0.37	0.68	0.99	0.93
15	B.M.	F	23	7.5	3.92	0.37	1.01	1.05	1.11
16	M.N.	F	18	7.55	3.52	0.21	0.91	1.41	1.37
17	O.N.	M	41	7.5	3.87	0.19	0.66	0.99	1.75
18	M.O.	F	20	7.28	3.93	0.13	0.62	0.81	1.63
19	V.P.	F	42	7.3	5.11	0.19	0.48	0.55	0.96
20	D.R.	F	16	7.15	3.93	0.35	0.61	0.73	1.54
21	W.S.	F	67	6.3	3.63	0.15	0.77	0.57	1.08
22	M.S.	F	19	5.8	2.47	0.34	0.99	1.24	0.59
23	E.S.	F	49	6.5	3.78	0.20	0.66	0.79	0.96
24	E.S.	F	54	6.3	2.94	0.16	0.88	1.05	1.22
25	H.T.	M	61	8.0	4.93	0.31	0.59	0.69	1.30
26	T.W.	F	54	6.8	2.97	0.18	0.78	1.37	1.54
27	J.W.	M	55	6.6	3.16	0.19	0.59	1.00	1.66
28	H.W.	M	54	7.2	4.03	0.18	0.72	0.99	1.22
29	G.Y.	M	19	8.0	3.54	0.19	0.59	1.45	2.18
		MEAN		7.06	3.72	0.24	0.75	0.98	1.26

APPENDIX H

THE CONCENTRATIONS OF SERUM PROTEIN FRACTIONS IN 41 'CONTROLS'

No.	Pt.	Sex	Age	Total Prot.	Album.	Alpha-1 Glob.	Alpha-2 Glob.	Beta Glob.	Gamma Glob.
1	T.M.	M	31	9.1	4.28	0.33	0.80	1.42	2.22
2	J.	M	35	9.0	4.72	0.28	0.64	1.07	2.23
3	D.L.	M	35	9.1	5.05	0.21	0.96	1.26	1.56
4	S.P.	M	36	8.6	4.16	0.41	0.86	1.44	1.72
5	H.B.	M	35	9.4	4.37	0.45	1.30	1.75	1.47
6	D.	M	42	8.1	3.99	0.34	0.85	1.34	1.61
7	E.	M	50	7.5	4.47	0.25	0.78	1.00	1.03
8	R.	M	28	8.4	5.44	0.27	0.70	0.72	1.33
9	J.B.	M	30	8.6	5.16	0.31	0.45	1.17	1.58
10	J.K.	F	25	8.6	4.34	0.21	0.49	1.69	1.79
11	G.	F	24	7.5	3.75	0.30	0.84	0.84	1.80
12	Y.	F	23	7.6	4.15	0.31	1.09	1.04	1.35
13	J.E.	F	22	7.1	2.73	0.37	0.55	1.67	1.63
14	B.	F	29	6.5	3.12	0.32	0.94	1.11	0.90
15	L.S.	F	40	6.75	2.63	0.41	1.00	1.22	1.55
16	S.	M	38	7.4	3.18	0.27	1.38	1.27	1.22
17	J.	F	36	6.9	4.38	0.10	0.58	0.94	0.92
18	M.	F	49	7.5	4.01	0.30	0.86	0.86	1.43
19	C.	M	51	7.3	4.22	0.38	0.62	0.86	1.27
20	S.D.	F	42	7.0	4.31	0.18	0.47	1.01	1.04
21	M.M.	M	40	7.8	4.26	0.15	0.72	0.72	1.95
22	V.T.	M	32	7.7	4.72	0.31	0.71	0.72	1.18
23	J.L.	M	31	6.56	4.28	0.22	0.41	0.64	1.01
24	P.G.	M	35	8.0	5.42	0.17	0.66	0.62	1.10
25	M.R.	F	42	7.8	5.43	0.23	0.70	0.56	0.85
26	M.K.	F	26	8.0	5.22	0.22	0.78	0.66	1.10
27	J.M.	F	24	7.7	4.85	0.29	0.43	0.77	1.36
28	C.H.	F	25	8.0	5.36	0.14	0.53	0.82	1.14
29	I.N.	F	24	8.28	4.50	0.34	0.62	0.95	1.88
30	M.S.	F	30	7.28	4.30	0.40	0.34	1.03	1.20
31	M.M.	F	23	7.44	4.88	0.18	0.49	0.76	1.13
32	D.H.	F	23	7.5	3.94	0.38	0.94	0.79	1.43
33	S.	M	43	7.5	4.40	0.32	0.86	1.25	1.46
34	W.	F	30	6.8	4.11	0.10	0.78	0.92	0.91
35	J.	M	50	8.0	4.82	0.22	0.90	1.18	1.08
36	F.	M	32	7.1	3.41	0.40	0.55	1.53	1.06
37	L.B.	F	31	7.0	4.21	0.21	0.54	1.02	1.04
38	R.K.	M	34	6.75	3.98	0.41	1.01	0.68	0.82
39	C.	M	32	6.5	3.25	0.26	0.94	1.16	0.77
40	J.	M	55	8.6	5.16	0.30	0.46	1.26	1.51
41	S.C.	M	58	7.0	4.38	0.21	0.39	0.91	1.03
		MEAN		7.69	4.33	0.28	0.73	1.04	1.33

APPENDIX J

IMMUNIZATION SCHEDULE

Study Day	Antigens	Dose
0	(Blood sample drawn)	
1	Staphage lysate	0.05 ml. S.C.
	Mumps vaccine	1.0 ml. S.C.
	Diphtheria toxoid	0.05 ml. I.M.
2	Influenza vaccine	1.0 ml. I.M.
	Typhoid-paratyphoid vaccine	0.5 ml. S.C.
4	Staphage lysate	0.1 ml. S.C.
8	Mumps vaccine	1.0 ml. S.C.
	Staphage lysate	0.1 ml. S.C.
9	Typhoid-paratyphoid vaccine	0.5 ml. S.C.
12	Staphage lysate	0.3 ml. S.C.
16	Staphage lysate	0.4 ml. S.C.
	Typhoid-paratyphoid vaccine	0.5 ml. S.C.
18	Diphtheria toxoid	0.5 ml. I.M.
20	Staphage lysate	0.5 ml. S.C.
32	(Blood sample drawn)	

S.C. = administered subcutaneously
I.M. = administered intramuscularly